March 20, 2003

Frederick R. Johannsen
Technical Contact
Solutia, Inc.
575 Maryille Centre Drive
St. Louis, MO 63141

Dear Mr. Johannsen:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 4,5,6,7-Tetrachloro-1,3-isobenzofurandione posted on the ChemRTK HPV Challenge Program Web site on November 20, 2002. I commend Solutia, Inc. for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Solutia, Inc. advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
4,5,6,7-Tetrachloro-1,3-isobenzofurandione (Tetrachlorophthalic anhydride)

Summary of EPA Comments

The sponsor, Solutia, Inc., submitted a test plan and robust summaries to EPA for 4,5,6,7-tetrachloro-1,3-isobenzofurandione (tetrachlorophthalic anhydride or TCPA, CAS No. 117-08-8) dated November 6, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on November 20, 2002.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

2. Environmental Fate. The submitter needs to provide measured stability in water (hydrolysis) data for this chemical and fugacity data on the hydrolysis product, tetrachlorophthalic acid. Although the data for indirect photooxidation are adequate, EPA recommends that the submitter provide data or a technical discussion for direct photolysis.

2. Health Effects. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. However, the submitter needs to address deficiencies in some robust summaries.

3. Ecological Effects. The submitted data are inadequate. It may be preferable to perform chronic aquatic toxicity testing; however, EPA reserves judgment on the ecological effects endpoints pending the outcome of hydrolysis testing.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the 4,5,6,7-Tetrachloro-1,3-isobenzofurandione Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The data provided by the submitter for melting point, boiling point, water solubility, vapor pressure and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

Photodegradation. The data provided by the submitter are adequate for the purposes of the HPV Challenge Program. Because this chemical will absorb light at wavelengths > 290 nm (Weast 1979), EPA recommends that the submitter consider developing aquatic photolysis data on TCPA or the hydrolysis product or provide a technical discussion explaining the relative importance of this fate pathway.

Stability in water. The submitter states that TCPA will readily hydrolyze in water to the diacid. The submitter further states that the electron-withdrawing chlorine atoms should increase the susceptibility to base hydrolysis relative to the parent compound phthalic anhydride (reported half-life in water, 90 sec) by reducing electron density and increasing the reactivity at the carbonyl carbon. This reasoning is inadequate without supporting data such as hydrolysis rates of other halogenated phthalic anhydrides.

The submitter also reports that the structurally similar tetrabromophthalic anhydride hydrolyzes "rapidly" in moist soils. This potentially useful information cannot be evaluated because the submitter did not provide study details in a robust summary.

Thus, EPA does not agree that the submitted data adequately support a conclusion that TCPA hydrolyzes comparably to phthalic anhydride under environmentally relevant conditions. EPA also disagrees with the contention that the study is impractical to conduct because the OECD Guideline 111 test requires the test material to be soluble at a level of 20 mM, whereas the solubility of TCPA cited in the test plan is < 0.004 mM. OECD 111 indicates how to proceed if the water solubility is less than 2×10^{-2} M. The submitter needs to provide more convincing data to support its case that testing is not necessary or provide measured stability in water data for this chemical following OECD Guideline 111. Clarification of the hydrolysis behavior is also important for design and interpretation of ecotoxicity testing.

Finally, the submitter needs to present all information related to stability in water in robust summary format.

Biodegradation. The data provided by the submitter for biodegradation are adequate for the purposes of the HPV Challenge Program.

Transport and distribution (fugacity). The data provided by the submitter for transport and distribution are adequate for the purposes of the HPV Challenge Program. However, since this chemical hydrolyzes (at a rate that needs better definition, as discussed above) to tetrachlorophthalic acid, the submitter needs to provide transport and distribution data for the acid as well.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available for all health-related endpoints for the purposes of the HPV Challenge Program.

Repeated-Dose Toxicity. Table 5 on page 13 of the Test Plan inappropriately includes entries for oral and inhalation NOELs that are below the levels tested. The appropriate entry is "none or not established." It would be appropriate to include the LOAEL values in the table with the caveat "lowest dose tested."

Reproductive Toxicity. The endpoint is addressed by documentation of the evaluation of reproductive organs in a 13-week repeated-dose toxicity study and the availability of an adequate existing developmental toxicity study. However, the submitter needs to provide more information in the reproductive toxicity robust summary relative to this issue. For example, note the repeated-dose study organ weight/pathological findings for the reproductive organs.

Ecological Effects (fish, invertebrates, and algae).

EPA reserves judgment on whether the ecological endpoints have been met pending the outcome of a hydrolysis study that will help determine what substances the test organisms are exposed to. However, in its review thus far, EPA has concluded that the submitted toxicity studies are inadequate for the purposes of the HPV Challenge Program; in all cases, the tests were conducted at concentrations above the reported measured water solubility of TCPA and its proposed analog, tetrabromophthalic anhydride.

Given the calculated log partition coefficient value of 4.65 - which exceeds the 4.2 value used by EPA to suggest that effects are more likely following chronic exposure conditions rather than acute exposure conditions - EPA believes that it may be preferable to conduct chronic aquatic toxicity testing rather than further acute studies, depending on the outcome of hydrolysis testing.

Specific Comments on the Robust Summaries

Health Effects.

The submitter needs to provide the composition of the test material for all studies.

Acute Oral Toxicity. The summary lacks the incidences of clinical signs by dose and sex.

Genetic Toxicity (Gene Mutations). The criteria for judging the experimental outcome are missing.

Ecological Effects.

The ECOSAR data submitted used a log partition coefficient value of 3.57 (estimated). The reference provided was not complete (Leo, 1978. "Report on the Calculation of octanol/water Log P values for structure in EPA Files" - no journal, report, book or other citation is listed and it is not in the list of references). Another value provided in the submitter's robust summary was 4.65 - estimated using EPIWIN which is also used by EPA. Given this information, EPA believes the 4.65 value is the appropriate input value for an ECOSAR estimation.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

References

Weast, RC (ed). 1979. *Handbook of Chemistry and Physics*. 60th Edition. CRC Press, Boca Raton, FL, p. C-438.